Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-3, 6-17, 20-24, 27-37, 73-77, 79-82, 106-109, 112, 140, 143-153 and 155-174 are pending in the application, with claims 1, 15, 22, 157, 158 and 161 being the independent claims. Claim 154 is sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 1, 15, 22, 158 and 161 are sought to be amended. No new matter is added by way of these amendments. It is respectfully requested that the amendments be entered and considered.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Support for Claim Amendments

Support for the amendment to claims 1, 15, 22, 158 and 161 can be found throughout the specification, for example, at page 59, line 17, through page 61, line 2.

II. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 6-17, 20-22, 27-37, 73-77, 140, 154, 158 and 162 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. *See* Office Action, page 3. According to the Examiner:

> the specification, while being enabling for a polyanionic compound which is a polysulfonated or polysulfated compound as in claim 2, and for the use of a serum free or protein free medium, does not reasonably provide enablement for a polycationic compound or other polyanionic compound, and for a medium that is not serum or protein free.

Office Action, page 3. Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office. . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original).

Here, the Examiner has not provided any evidence or sound scientific reasoning to support the assertion that methods of the invention which comprise the use of a polycationic compound or a polyanionic compound, other than a polysulfonated or polysulfated compound, are not enabled. Nor has the Examiner provided any evidence or sound scientific reasoning to support the assertion that methods of the invention which comprise the use of a medium which is not serum-free or protein-free are not enabled. Therefore, a *prima facie* case of non-enablement has not been established.

Applicants do not agree that the methods of the invention which comprise the use of a medium which is not serum-free or protein-free are not enabled. Nonetheless, it is noted

that independent claims 1, 15 (as currently presented), 22, 158 and 161, all specify that the culture medium is serum-free. Thus, the enablement rejection, insofar as it relates to methods which comprise the use of a medium which is not serum-free or protein-free, is moot.

The Examiner asserted that "[t]here is no disclosure in the specification as to how one of skill in the art would practice the claimed invention using a polycationic compound or another polyanionic compound and a medium that is not serum or protein free." Office Action, page 3. Applicants respectfully submit that this is an incorrect statement. The specification teaches that, according to the present invention, a mammalian cell can be cultivated in suspension *in vitro* by: (a) obtaining a mammalian cell to be cultivated in suspension; and (b) contacting the cell with a serum-free cell culture medium comprising at least one polyanionic or polycationic compound, wherein the medium supports the cultivation of the cell in suspension. *See, e.g.*, specification at page 12, line 24, through page 13, line 1.

Thus, to practice the methods of the invention using a medium comprising at least one polycationic compound or at least one polyanionic compound -- including a non-polysulfonated or non-polysulfated polyanionic compound -- the specification teaches that the mammalian cell to be cultivated in suspension is simply contacted with the medium that contains such compounds. The specification therefore provides disclosure as to how one of skill in the art would practice the full scope of the claimed invention encompassed by claims 1, 6-17, 20-22, 27-37, 73-77, 140, 154, 158 and 162.

The Examiner acknowledged that methods comprising the use of a medium comprising a polysulfonated or polysulfated polyanionic compound *are* enabled. *See* Office Action, page 3. The Examiner has not explained why it is believed that practicing the methods of the invention using a medium comprising a polycationic compound or a non-polysulfonated or non-polysulfated polyanionic compound would be any different from practicing the methods of the invention using a medium comprising a polysulfonated or polysulfated polyanionic compound. The Examiner, however, stated that:

> There would be a high degree of unpredictability in this art to carry out the claimed method *for any mammalian cell type* using a polycationic compound since there are no examples disclosed in the instant specification to demonstrate that the same can be performed with any predictable positive outcome for viable cell recovery.

Office Action, page 3 (emphasis in original).

The Examiner has not explained why it is believed that there would be a "high degree of unpredictability in this art." No evidence has been presented to support this assertion. The Examiner simply stated that "there are no examples disclosed in the instant specification to demonstrate that the same can be performed with any predictable positive outcome for viable cell recovery." The absence of a working example in the specification, however, does not in any way suggest unpredictability in the art. Moreover, the Examiner is respectfully reminded that the absence of a working example in the specification cannot by itself form the basis of a rejection for lack of enablement. *See, e.g., Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987) ("The mere fact that something has not

previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it.")

Since the Examiner has not provided any evidence or sound scientific reasoning to support the assertion that the methods of the invention comprising the use of a medium comprising a polycationic compound or a non-polysulfonated or non-polysulfated polyanionic compound are not enabled, a *prima facie* case of non-enablement has not been established. Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

III. Claim Rejections Under 35 U.S.C. § 102

Claims 1-3 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,707,832 to Mignot *et al.* ("Mignot"). *See* Office Action, page 4. Applicants respectfully traverse this rejection.

An anticipation rejection under 35 USC § 102 requires a showing that each element of a claim is found in a single reference, practice, or device. *See In re Donohue*, 766 F.2d 531, 226 USPQ 619, 621 (Fed. Cir. 1985). Not every element of claims 1-3 is taught in Mignot. Therefore, Mignot cannot and does not anticipate claims 1-3.

Independent claim 1, as currently presented, is directed to a method of cultivating a mammalian cell in suspension *in vitro*. The method of claim 1 comprises: (a) obtaining a mammalian cell to be cultivated in suspension; (b) contacting the cell with a serum-free, chemically defined cell culture medium comprising at least one polyanionic or polycationic

compound, wherein the medium supports the cultivation of the cell in suspension, with the proviso that the medium does not contain dextran sulfate; and (c) cultivating the cell in suspension in the medium.

Mignot does not teach a method comprising cultivating a mammalian cell *in suspension*. Rather, Mignot refers to the production of the blood coagulating agent known as factor VIII from recombinant cells in culture. Mignot mentions that "recombinant CHO cells which express factor VIII or analog of factor VIII in a continuous manner" can be used for the production of factor VIII. *See* Mignot, column 4, lines 3-6. Mignot, however, does not teach the use of CHO cells that have been adapted to suspension culture. In fact, there is no mention of culturing cells in suspension at all in Mignot.

Since Mignot does not teach cultivating a mammalian cell in suspension, Mignot does not and cannot anticipate claims 1-3. Applicants respectfully request that the rejection under 35 U.S.C. § 102 be reconsidered and withdrawn.

IV. Claims Rejections Under 35 U.S.C. § 103

A. Mignot in view of Chessebeuf, Parenteau and Cleveland

Claims 6-14, 22-24, 27-32, 35-37, 140, 154 and 157-160 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Mignot in view of U.S. Patent No. 4,786,599 to Chessebeuf *et al.* ("Chessebeuf"), U.S. Patent No. 5,712,163 to Parenteau *et al.* ("Parenteau") and U.S. Patent No. 4,767,704 to Cleveland *et al.* ("Cleveland"). *See* Office Action, page 6. Applicants respectfully traverse this rejection.

A *prima facie* case of obviousness cannot be established unless all of the claim elements are taught or suggested by the cited references. *See In re Royka*, 490 F.2d 981, 984-85 (CCPA 1974); *see also In re Glaug*, 283 F.3d 1335, 1341-42 (Fed. Cir. 2002); *In re Rijckaert*, 9 F.3d 1531, 1533 (Fed. Cir. 1993). In addition, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Since not all of the elements of claims 6-14, 22-24, 27-32, 35-37, 140, 154 and 157-160 are taught or suggested by the cited references, and since a person of ordinary skill in the art would not have been motivated to modify or combine the cited references, a *prima facie* case of obviousness has not been established.

1. Claims 6-14, 22-24, 27-32, 35-37, 140 and 158

An element of currently presented claims 6-14, 22-24, 27-32, 35-37, 140 and 158[1] is cultivating a mammalian cell in suspension. None of the cited references teach or suggest cultivating a mammalian cell in suspension.

Mignot indicates that the culture medium of this reference contains at least one derivative of a polycationic and/or polyanionic polymer. *See* Mignot, column 2, lines 25-31. According to Mignot, the polycationic and/or polyanionic polymer is included, not to facilitate the culture of cells in suspension, but to enhance the production of factor VIII. *See* Mignot, column 3, lines 60-63. There is no indication or suggestion that the cells used in

[1] Claim 154 has been cancelled.

Mignot were cultivated in suspension. In fact, the examples in Mignot strongly suggest that the cells were plated to substrates. (*See, e.g.*, Mignot, column 5, lines 20-22, indicating that the cells were grown in six-well plates and that the medium was changed every 24 hours -- conditions that are typically used for adherent cell culture and that are inappropriate for suspension culture.) As mentioned above, there is no mention of culturing cells in suspension in Mignot at all.

Likewise, neither Chessebeuf, Parenteau nor Cleveland teach or suggest cultivating a mammalian cell in suspension. Chessebeuf and Parenteau teach the necessity of a "substratum" or "substrate" upon which the cells of these references are plated. *See* Chessebeuf, column 5, lines 19-40, and Parenteau, column 5, lines 61-67. Since cells that have been plated to a substratum are, by definition, not cultured in suspension, Chessebeuf and Parenteau necessarily exclude the suspension culture of cells. Similarly, Cleveland notes that the culture medium of this reference "facilitates attachment of cells to substratum," and indicates that "[t]his is true even for cell lines which grow unattached in other media." *See* Cleveland, column 11, lines 64-68. Thus, the medium of Cleveland would not permit suspension culture, even for cells that have been specifically adapted to growth in suspension.

Neither Mignot, Chessebeuf, Parenteau, nor Cleveland teach or suggest cultivating a mammalian cell in suspension. Since this is an element of claims 6-14, 22-24, 27-32, 35-37, 140 and 158, and is not taught or suggested by the cited references, a *prima facie* case of obviousness has not been established.

2. Claims 157, 159 and 160

Claims 157, 159 and 160 are directed to methods for replacing protein in a mammalian cell culture medium. The methods comprise replacing insulin with a Zn^{2+} salt *and* replacing transferrin with a Fe^{2+} chelate and/or a Fe^{3+} chelate.

None of the cited references teach or suggest replacing insulin with a Zn^{2+} salt. Since not all elements of claims 157, 159 and 160 are taught or suggested by the cited references, a *prima facie* case of obviousness has not been established.

B. Mignot in view of Chessebeuf, Parenteau, Cleveland and Wang

Claims 33, 34, 73-77 and 161-174 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Mignot in view of Chessebeuf, Parenteau, Cleveland and U.S. Patent No. 5,872,005 to Wang *et al.* ("Wang"). *See* Office Action, page 8. Applicants respectfully traverse this rejection.

Claims 33, 34 and 161-174 depend from claims 1, 15 and 22 which are directed to methods of cultivating a mammalian cell in suspension *in vitro*. The methods of claims 33, 34 and 161-174 therefore comprise cultivating a mammalian cell in suspension. Claims 73-77 are directed to methods of producing a virus. The methods of claims 73-77 comprise, *inter alia*, cultivating a mammalian cell according to the method of any one of claims 1, 15 or 22. Thus, an element of each of claims 33, 34, 73-77 and 161-174 is cultivating a mammalian cell in suspension. None of the cited references teach or suggest cultivating a mammalian cell in suspension.

As noted above, neither Mignot, Chessebeuf, Parenteau, nor Cleveland teach or suggest cultivating a mammalian cell in suspension. *See* Section IV.A.1, above. Likewise, Wang only refers to the culture of attached cells, *see, e.g.*, column 11, lines 59-63, and does not teach or suggest the culture of mammalian cells in suspension. Since not all elements of claims 33, 34, 73-77 and 161-174 are taught or suggested by the cited references, a *prima facie* case of obviousness has not been established.

C. There Would Have Been No Motivation to Combine the References

In addition to the fact that not all elements of the claims are taught or suggested by the cited references, Applicants note that a person of ordinary skill in the art would not have been motivated to combine or modify the cited references. To establish a *prima facie* case of obviousness, the Examiner must present "clear and particular" evidence of a motivation to combine the references. *See In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). "Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" *Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617.

Here, the Examiner has not pointed to anything specific that would suggest combining the references. The Examiner has simply made several unsupported conclusory assertions. For example, with regard to the rejection of claims 6-14, 22-24, 27-32, 35-37, 140, 154 and 157-160 based on Mignot, Chessebeuf, Parenteau and Cleveland, the Examiner stated that "[o]ne of skill in the art would have been motivated by the prior art to cultivate mammalian cells by contacting them with these well known ingredients in culture medium

as disclosed by the prior art." Office Action, page 8. No explanation or evidence was presented to support this assertion.

With respect to the rejection of claims 33-34, 73-77 and 161-174 based on Mignot, Chessebeuf, Parenteau, Cleveland and Wang, the Examiner stated that "[c]learly one of skill would have been motivated to select for 293 cells which would have been a choice of functional equivalents available to the artisan." Office Action, page 9. Again, no evidence or explanation has been presented to support this assertion. A rejection under § 103 cannot be based on unsupported assertions regarding the supposed combinability of the cited references.

Since not all elements of the claims are taught or suggested by the cited references, and since a person of ordinary skill in the art would not have been motivated to combine or modify the cited references, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be reconsidered and withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that

personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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